Scientific Advisory Group for the Origins of Novel Pathogens (SAGO)

Preliminary Report of the SAGO

9 June 2022

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*This version includes a timeline, letters to WHO from the SAGO, and clarifications requested by WHO.

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Contents

Acronyms and abbreviations

FAO	Food and Agriculture Organization of the United Nations
ILI	Influenza-like Illness
MERS	Middle East Respiratory Syndrome
OHHLEP	One Health High-Level Expert Panel
OIE	World Organisation for Animal Health
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAGO	Scientific Advisory Group for the origins of novel pathogens
VOC	Variants of concern
WHO	World Health Organization

1. Executive summary

This is the first preliminary report from the scientific advisory group for the origins of novel pathogens (SAGO) to WHO and represents work that is ongoing and not yet complete. The work of the SAGO should be read as a work in progress. Further reports by the SAGO will be provided as discussions continue.

This first report focuses on providing initial recommendations for the development of a global framework to study emerging and re-emerging pathogens of pandemic potential and preliminary recommendations on urgent studies needed to better understand the origins of the COVID-19 pandemic. The report provides background information about the formation and meetings of the SAGO since it was established on 13 October 2021, including an overview of some of the scientific discussions members have had in plenary and as part of technical working groups of the SAGO. The second version of the report includes a timeline, letters to WHO from the SAGO, and clarifications requested by WHO.

The SAGO emphasizes that its work has only just begun. The SAGO is a scientific advisory group and is firmly focused on science and public health. It is operating under the agreed terms of reference and will continue to fulfil the objectives outlined therein. This report highlights important elements that will need to be considered as part of a global framework to inform the actions needed each time an emerging or re-emerging pathogen is identified and causes human infections. The SAGO will continue to discuss and provide detailed recommendations towards the development of the global framework.

The elements recommended by the SAGO to make up a global framework currently include:

- early investigation studies and anthropology
- human studies
- animal/human interface
- environmental studies and ecological studies
- genomics and phylogenetics
- biosafety and biosecurity

The SAGO–using these proposed elements of a global framework to study the emergence of a novel pathogen–offers preliminary recommendations to advance our understanding of the emergence of SARS-CoV-2 into the human population. The SAGO has reviewed available findings to date and notes that there are key pieces of data that are not yet available for a complete understanding of how the COVID-19 pandemic began.

Within this report, key recommendations are provided for further studies needed on humans, animals and the environment in China and around the world that would provide additional information and contribute to a better understanding of how SARS-CoV-2 infected the human population and spread. At the present time, currently available epidemiological and sequencing data suggest ancestral strains to SARS-CoV-2 have a zoonotic origin with the closest genetically related viruses being beta coronaviruses, identified in Rhinolophus bats in China in 2013 (96.1%) and Laos in 2020 (96.8%). However, so far neither the virus progenitors nor the natural/intermediate hosts or spill-over event to humans have been identified. Early investigations suggested that the Huanan seafood market in Wuhan played an important role early in the amplification of the pandemic with several of the patients first detected in December 2019 having had a link to the market and environmental samples from the market testing positive for

SARS-CoV-2. There are, however, further studies needed to follow up on several gaps in our knowledge. For example, the source of SARS-CoV-2 and its introduction into the market is unclear and it is yet to be determined where the initial spill over event(s) occurred. There is a need to examine environmental samples collected from specific stalls and drains at the market in January 2020 that tested positive for SARS-CoV-2 in areas known to have sold live animals. Furthermore, follow-up studies to identify possible animal sources from which the environmental contamination could have originated from have not been completed. Other essential studies include detailed mapping of upmarket trade of wild/domestic animals sold in Wuhan City and Hubei Province and clinical history and seroprevalence of SARS-CoV-2 antibodies in humans and animals from the source farms of animals sold at Wuhan markets.

In addition, further verification analyses of human samples collected through national surveillance programs, including Influenza and other respiratory samples (e.g., RSV and enterovirus D68) during the months prior to December 2019 are still needed in China and worldwide. Genetic studies of coronaviruses in wildlife species in Asia and the rest of the world are also needed in order to identify new leads on ancestral or intermediate hosts (such as animals that have been identified as susceptible throughout the pandemic).

The SAGO notes that there has not been any new data made available to evaluate the laboratory as a pathway of SARS-CoV-2 into the human population and recommends further investigations into this and all other possible pathways. The SAGO will remain open to any and all scientific evidence that becomes available in the future to allow for comprehensive testing of all reasonable hypotheses.

This first report of the SAGO contains preliminary recommendations for both the global framework and its application to SARS-CoV-2, specifically, based on available published evidence and the initial deliberations of the SAGO. Dividing into technical working groups organized around the six elements of the global framework, SAGO members have met to review and discuss available evidence and information presented to them and have made recommendations on the urgent studies needed to better understand the origins of SARS-CoV-2 in China and other countries. This preliminary report is not intended to, nor does it, provide conclusive findings on the origins of SARS-CoV-2 because more information is needed from the studies recommended in this report.

The SAGO has not been formed to find the origins of SARS-CoV-2 but rather has been tasked with advising studies that are necessary to gather evidence to better understand the origins of SARS-CoV-2, and more broadly, origins of emerging and re-emerging future epidemics/pandemics. The SAGO will continue to meet regularly and discuss emerging evidence and looks forward to reviewing findings from the studies recommended here within and providing further advice to WHO.

2. Background information on the establishment of the SAGO

In May 2020, the World Health Assembly 73.1 approved Resolution 6, which identified the need for WHO to work with partner agencies including the World Organisation for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO). The aim was to strengthen WHO's internal coordination of One Health-related activities as it sought to identify the source of SARS-CoV-2 and the route of introduction into the human population. Understanding the source of a virus emergence that leads to a pandemic is difficult yet crucial to understanding how to prevent a similar event in the future.

In response to this resolution, on 14 July 2021, the WHO Director-General announced the establishment of a scientific advisory group for the origins of novel pathogens (SAGO). The SAGO is meant to advise WHO on technical and scientific considerations regarding the origins of emerging and re-emerging pathogens. Through a One Health approach, the SAGO will recommend studies needed to explore how novel pathogens move from reservoirs to intermediate hosts and ultimately to humans and how these same pathogens can jump back from humans to animals.

The SAGO is composed of experts acting in a personal capacity and works with additional experts from various technical areas as needed.

The establishment of the SAGO followed WHO's policies and procedures for setting up an advisory group. The initial open call for applications for membership for this scientific advisory group was released on 20 August 2021 and was widely circulated across all WHO offices, networks and through the media and social media. The selection process was completed following two further open calls for applications.

A selection panel was convened and led by Dr Mike Ryan, Executive Director of the WHO Health Emergencies division and Dr Maria Van Kerkhove, Head of the Emerging Diseases and Zoonoses unit and Technical Lead for COVID-19.
The panel assessed applications according to the following criteria:

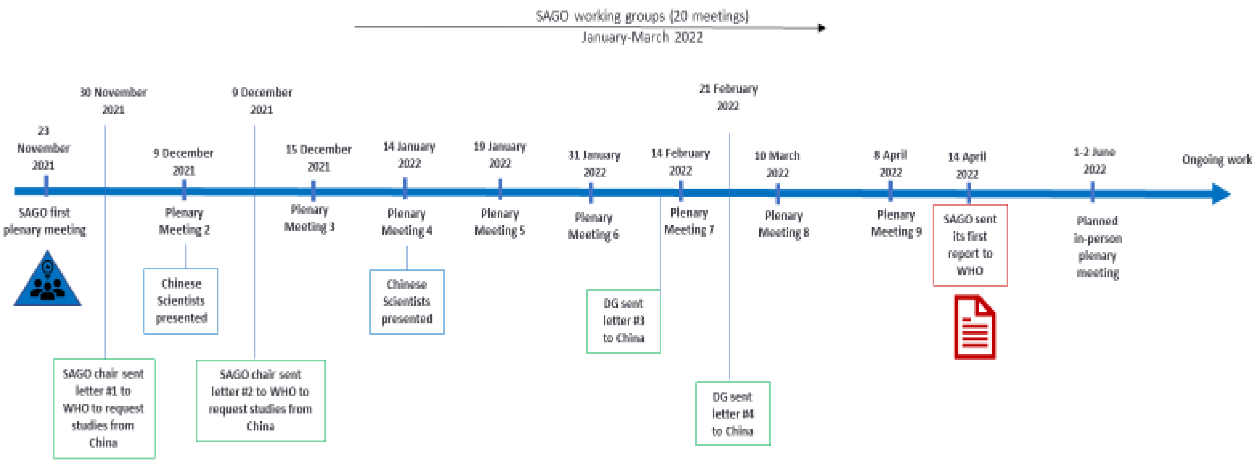
- technical/subject matter expertise in one or more of the required fields mentioned in the terms of reference
- research experience related to emerging and re-emerging pathogens
- experience in conducting field investigations
- experience in complex international public health response
- breadth of professional expertise based on working across disciplines
- experience on other WHO advisory groups
- highest educational level
- nationality and geographic diversity
- gender
- current and past affiliations
- relevant declarations of interest.

According to WHO policies and procedures, the WHO Secretariat reviewed and ranked more than 800 applications for appropriate technical expertise and ensured various disciplines were represented and that there was balanced gender and geographical representation. In addition, the WHO Secretariat reviewed applicants' completed declaration of interest forms to ensure proposed members did not have a conflict of interest or possible intellectual bias.

On 13 October 2021 the Director-General announced the appointment of the SAGO's 27 members (see Annex 1). This geographically diverse and gender-balanced group encompasses wide-ranging technical expertise (infectious disease epidemiology, field research, virology, ecology, molecular epidemiology, sero-epidemiology, medicine, bioinformatics, outbreak analytics, microbiology, veterinary medicine, food safety, bacteriology, environmental science and biosafety/biosecurity).

At the first meeting of the SAGO on 23 November 2021, the Director-General appointed Prof Marietjie Venter as the Chair of the SAGO and Dr Jean-Claude Manuguerra as Vice Chair.

Figure 1. Timeline of SAGO meetings and information requested.



SAGO aims and objectives

In its capacity as an advisory body to WHO, the SAGO will follow its terms of reference as outlined at the time of its creation and will have the following functions.

1. The main objective of the SAGO will be to advise WHO on the development of an overarching global framework to define and guide studies into the origins of emerging and re-emerging pathogens of epidemic and pandemic potential. The resulting global framework can be implemented by countries in the context of an emerging threat.
2. The group has been mandated with identifying and prioritizing required studies and field investigations into the origins of emerging and re-emerging pathogens.
3. The SAGO shall develop a detailed work plan for its functioning.
4. In the context of SARS-CoV-2, the functions of SAGO are to
    a. provide the WHO Secretariat with an independent evaluation of the available scientific and technical evidence from global studies
    b. advise WHO regarding developing, monitoring, and supporting next steps regarding studies in the origins of SARS-CoV-2, including advice on implementing next studies into origins of SARS-CoV-2 outlined in the WHO-convened global study of origins of SARS-CoV-2: China Part published March 2021
    c. provide advice regarding future international missions related to the study of SARS-CoV-2.

SAGO working groups

To help achieve its objectives, the SAGO meets regularly in plenary with all members as well as within the six technical working groups the members have organized themselves into, each of which focusses on a technical element that will serve to develop and guide the global framework.

The six working groups currently are:

- early investigation and anthropology studies
- human studies
- animal/human interface studies
- environmental and ecological studies
- genomics and phylogenetics studies
- biosafety and biosecurity studies.

SAGO meeting proceedings

The SAGO has held eight plenary meetings between 23 November 2021 and 14 February 2022 (see Annex 2 for the full list). The six working groups have also met an additional 20 times in total since being formed to review existing evidence and discuss the preliminary recommendations included in this report.

The first SAGO plenary meeting on 23 November 2021 outlined the policies and procedures for setting up WHO advisory groups as per WHO protocols. The SAGO received presentations by the SAGO Secretariat, WHO Office of the Legal Counsel; the Compliance, Risk assessment and Ethics department; the WHO Communications department; and other WHO advisory groups. Subsequent meetings provided overviews of the work currently being conducted by WHO teams on various high-threat or high-consequence pathogens such as SARS-CoV, SARS-CoV-2, MERS-CoV, Ebola virus, Marburg virus and arboviruses; and WHO's work on biosafety and biosecurity.

In order for the SAGO to properly evaluate available evidence related to the origins of SARS-CoV-2, the WHO secretariat presented the SAGO with an overview of available published and pre-published literature. In addition, the SAGO chair made two requests to the WHO SAGO secretariat on 30 November 2021 and 9 December 2021 (Annex 3) requesting information from Chinese scientists on the status of the recommendations included in the 2021 WHO-China Joint Report, and to invite Chinese scientists to present updated findings from studies conducted since March 2021 at the 2nd and 4th plenary meetings of the SAGO. Following receipt of these letters WHO invited Chinese scientists to present their research findings on 9 and 14 December 2021. They provided presentations of work evaluating animal and environmental studies, the role of the cold-chain in the introduction of SARS-CoV-2 to markets, molecular studies and one SARS-CoV-2 serosurvey using stored sera from blood donors in Wuhan collected in 2019.

In addition, the WHO Director-General, Dr Tedros Adhanom Ghebreyesus sent two letters to His Excellency Mr Li Keqiang and Minister Ma Xiaowei on 14 February 2022 and 21 February 2022 respectively, requesting information on the status of studies evaluating the earliest investigations around suspected human cases in Wuhan, China, the results of serologic testing of 2019 biologic samples and occupationally exposed workers from farms that supplied the animal markets in Wuhan and Hubei province, the results of traceback studies and further information into the laboratory hypotheses.

It is important to note that at the time of writing, there are outstanding results from the recommended studies from the 2021 Joint Report, that the SAGO feels need to be conducted (and are further outlined later in this report). It is also important to note, the SAGO was not provided any information related to studies conducted evaluating the laboratory hypotheses as a possible introduction into the human population.

3. Preliminary recommendations

The SAGO offers preliminary recommendations in three areas:

1. The development of a global framework that will outline necessary studies to conduct once an emerging pathogen appears or re-appears
2. Preliminary recommendations for additional studies urgently needed to understand the origins of SARS-CoV-2
3. Areas to be explored concerning the emergence of SARS-CoV-2 variants of concern, such as Omicron.

The preliminary recommendations made by the SAGO for studying the origins of the COVID-19 pandemic are based on available published scientific findings (up to 10 March 2022) and technical discussions during SAGO meetings. The work of the SAGO is not yet complete, and these recommendations represent a work in progress.

3.1 Global framework to study emerging and re-emerging high-threat zoonotic pathogens

The rapid emergence and spread of SARS-CoV-2 has highlighted the importance of being prepared for a future event of a new "disease X", to be able to identify novel pathogens early and address the risk factors that contribute to the pathogen's emergence and spread. The emergence of SARS-CoV-2 has occurred in the context of an increasing number of high-threat pathogens emerging and re-emerging in recent years. These include viruses causing SARS, MERS, Lassa fever, Marburg fever, Ebola disease, Nipah encephalitis, avian influenza and polio; and arboviruses causing Dengue, Zika and Chikungunya, among others.

Consequently, there is a need for robust and comprehensive surveillance as well as early actions for rapid detection of these pathogens and mitigation efforts once they are detected. There is also a need for robust and systematic processes to establish the work necessary to investigate the emergence of these pathogens and the routes of transmission from their natural reservoirs to humans.

The global framework that the SAGO will advise on will outline relevant studies needed to investigate emerging epidemic and pandemic threats. It will include a comprehensive list of coordinated studies that need to be carried out when and where the (re)emergence is detected, using a holistic One Health approach.

As such, the SAGO is providing initial recommendations for the various elements that should be included in the global framework.

Context of "origin" and "source" in this report
In the context of this report, the "origin" can be understood as the ancestral host from where the pathogen has evolved. The "source" can be understood as any animal species or population susceptible to the infection, be it a reservoir or not. According to the definition of Haydon et al., "a reservoir is one or more epidemiologically connected populations or environments in which the pathogen can be permanently maintained and from which infection is transmitted to the defined target population" (Haydon et al., 2002) . The novel pathogens referred to in this context could be viruses, bacteria, parasites or fungi originating from animals, arthropods or the environment. There are several complex steps that allow a pathogen to be successful in its infiltration of the host and onward transmission to humans. These include first colonizing the host and finding a niche in the body that will allow the pathogen to infiltrate the host as it adapts to the immune responses, then replicating and exiting the body in order to spread to a new host. Understanding the modes of transmission of a pathogen are also important in implementing prevention and control responses.

3.1.1 Early investigation studies

Gathering information as quickly as possible from the earliest cases among humans, animals and the environment is critical for our understanding of the origin of a disease X at the time of its emergence. This may help to put in place prevention measures to prevent further transmission to humans or animal populations and prevent large-scale epidemics or pandemics. Additionally, it can help in designing specific One Health surveillance studies for the detection of future emergences. While early investigations are crucial at the onset of an outbreak, they rely heavily on the safe and effective collection, storage and sharing of critical samples needed for these studies.

Investigations of such samples provide crucial understanding of possible animal hosts or reservoirs associated with the earliest cases and the associated human behaviour/practices that may have increased the odds of acquiring the infection. An ideal investigation would involve the assembly of a response team in the country where the infection is first detected with assistance from international technical partners such as WHO and the Global Alert and Response Network (GOARN) to support such investigations (if applicable). Early investigations should include establishing support for existing lab systems for rapid and specific pathogen identification (e.g. diagnosis, isolation and genomic sequencing) and urgent epidemiology studies to generate data and evidence as fast as possible to avoid recall bias and loss of important information. Such data is pivotal for better understanding of the ongoing health emergency, and to inform targeted and effective actions as well as the overall response.

The global framework should include early investigation studies such as:

- epidemiologic investigations that identify the type of disease, modes of transmission, type of transmission; and the extent of human-to-human transmission and/or animal to human transmission, environment to human transmission or nosocomial transmissions occurring in health care settings or other closed settings

- studies to investigate early cases, including onset and nature of clinical signs, any travel history and exposures to animals or other sources of relevance
- plans for visits and systematic recording of information from the site(s) of the earliest detected cases
- investigations that will ensure early specimen collection and contribute to biobanking (humans, animals, environment samples).

3.1.2 Human studies

Human studies contribute to identifying the origins of novel pathogens by determining the initial clinical, epidemiological and microbiological features of a new disease and obtaining epidemiological information from early recognized cases that may indicate time, place and person aspects of initial transmission. Time-, place- and person-based regional analyses of syndrome- or event-based surveillance data can lead to additional hypotheses and avenues for investigation. Coordinated studies can link clinical, epidemiological, serological, anthropological and molecular sequencing data from early known cases and among clinically suspected retrospective cases to better understand their relatedness and common ancestry. An important step will be to design and develop legally approved frameworks to enable rapid sharing of all relevant data and ensure early specimen collection and contributions to biobanking.

The global framework should include human studies that:

- search for evidence of earlier (than reported) human infections and transmission due to a novel/re-emerging pathogen, including examination of data from routine human health event-based surveillance
- obtain epidemiological information from early recognized cases that may indicate time, place and person aspects of initial transmission to humans and from human to human
- search for other unrecognized early cases that might contribute additional early epidemiological information, such as potential nosocomial outbreaks
- use the development of diagnostics and the results of their use to understand the epidemiology of the clinical disease and transmission of infection
- link clinical, epidemiological and molecular sequencing data from early cases to better understand their relatedness and common ancestry
- share information from human epidemiological studies and information from studies of the human/animal interface, and environmental and anthropological studies
- contribute to the understanding of the emergence of new variants.

3.1.3 Animal and environmental studies

Studies evaluating direct and indirect exposures from wild and domestic animals

Studies evaluating direct and indirect exposures from wild and domestic animals should aim to identify the animal species susceptible to infection with the target pathogens and explore the chains of transmission between ancestral hosts, intermediate hosts and humans. The challenges to be addressed include the lack of standardized protocols for testing animals, since it is unclear which animals, in which settings and how many should be tested to ensure representativeness in the context of emergence of a novel pathogen. The SAGO recommends that such protocols should be developed by WHO in collaboration with its advisory groups including; the SAGO, One Health High-Level Expert Panel (OHHLEP)

and in consultation with the OIE and One Health experts as determined by the nature of the emerging/re-emerging pathogen.

The framework should include human and animal interface studies that:

- search for novel zoonotic pathogens from wildlife and domestic animals
- target surveillance of potential emerging zoonotic viruses
- include genome characterization of suspected novel zoonotic viruses
- determine the human risk of novel viruses isolated from/detected in wildlife
- study the susceptibility of animal species to a novel zoonotic virus to determine the host range and potential intermediate hosts
- seek to understand the spillover dynamic of novel zoonotic virus from wildlife to domestic animals and humans
- integrate epidemiological and molecular sequence data from animals (new and known) pathogens into human pathogen databases to better monitor their relatedness and ancestors in real time
- develop a sharing system of the database of novel pathogens detected in animals, humans and the environment among countries.

Environmental studies

The determination of transmission pathways, which may be dynamic from an environmental perspective–surface contamination, droplets, aerosols, airborne, water-borne, food-borne, through arthropod vectors–is critical for implementing early preventive and control measures during a pandemic. The SAGO notes that there is an untapped opportunity to define the design of studies for arthropod-borne diseases, including surveillance for vector incrimination, vectorial capacity, mapping and distribution of hosts and vectors and identification of weak points in the ecological cycle for intervention. Environmental sampling should include places with a high risk of transmission, such as (wet) markets, animal husbandry and breeding sites; slaughterhouses; dairy, fur and other animal-derived product manufacturing sites; and vehicles and equipment used to transport animals. Raw animal products–such as in the context of cold chains–should be considered for testing to identify possible routes of transmission and intermediate hosts.

Retrospective studies (human, animal, environmental samples)

Retrospective studies aim to examine an array of available stored samples (environmental, clinical, animals or insect vectors) that are needed to identify how far back in time the pathogen can be found and identify possible modes of transmission. High priority should be given to monitoring studies that collect biological samples among people and domestic animals.
An assessment should be conducted worldwide of routinely conducted surveillance programmes. This could include respiratory and enteric diseases in humans and animals (including biobanking and sequencing practices) to determine the potential utility of these specimens and what data are relevant to the investigation of the origins of novel pathogens.

3.1.4 Genomics and phylogenetics studies

Genomic and phylogenetic studies will contribute to identifying the origins of novel pathogens by estimating the number of independent virus founders during the early stages of an outbreak; inferencing the population dynamics of the virus and rates of viral spread; identifying infectious clusters; and tracing

transmission chains of resurgence. Genomics should be cross-cutting to identify closely related viruses in animal hosts as well as human samples, the environment and potential evolutionary mechanisms of emergence of novel viruses or variants.

This SAGO recommends that WHO continue to support and encourage countries to establish and/or enhance facilities to ensure early human sample collection and storage occurs and satisfies the requirements for large-scale sample sequencing and big data information analysis. The details, including sequencing protocols and platform, assembly methods and raw sequencing data should be submitted at the same time for quality assessment and re-analysis of data. The inclusion of genomic sequencing as a component of existing or emerging surveillance or research programmes in both humans and animals is encouraged and recommended.

Recent advances in genomic epidemiology during the COVID-19 pandemic should also be harnessed to enhance the reliability and timeliness of this information. This includes databases such as GISAID, Genbank and other national databases that host real-time genome sequences and epidemiological data for data sharing and cross-referencing purposes.

The framework should include studies that:

- review genomic data linked to the retrospective studies focusing on epidemiology in humans
- review genomic data and metadata linked to the studies focusing on animals, animal specimens and contaminated environments
- include phylogenetic analysis and evolutionary studies on the origins and transmission trajectory of new emerging pathogens.

3.1.5 The possibility of a breach in biosafety or biosecurity measures

During this pandemic and in past epidemics, there has been considerable discussion about the possibility of novel pathogens escaping into the human population due to a breach in biosafety or biosecurity in a laboratory or during field activities. Recognizing that historically this has unfortunately happened with other pathogens, it is important to include studies in the global framework that address these risks. A possible breach of biosafety or biosecurity measures may be caused by an accidental event or a procedural or engineering failure that results in the infection of staff working in a laboratory while handling animals or collecting specimens in a field setting. Such breaches in biosafety or biosecurity may also result in inadvertent or intentional release of pathogens from a laboratory into the human population or environment via direct or indirect means. Various precautions and regulations exist for laboratory and field work in some countries, but are still lacking in most low- and middle- income countries.

Broad areas to include in a global framework include review of biosafety programme administration, including risk-based assessment of biosafety and biosecurity measures for all pathogens and their associated activities. The global framework should cover pathogen storage and accountability, staff competency and training, as well as guidelines for creating and maintaining necessary facility structures and infrastructure to ensure the integrity of the biocontainment engineering facilities. The SAGO recognizes the need to work on these recommendations together with other WHO advisory groups, such as the Technical Advisory Group for Biosafety and others.

There is also the continued need for the identification and regulation of high-risk pathogen manipulation studies including 'gain of function' and 'dual use research of concern'. The SAGO proposes drawing upon existing documents such as the WHO Responsible life sciences research for global health security: a WHO guidance document and the Laboratory biosafety manual on Biosafety programme management for guidance on these recommendations.[1]

The SAGO proposes that following should be included in the global framework in this area:

- review of existing legislation and consideration of better national/institutional governance of complex experiments
- investigations of viruses with zoonotic potential being studied in an individual laboratory or programme of work
- investigations of biosafety programme management:
    - risk-based biosafety and biosecurity control measures based on known hazards associated with a pathogen and proposed laboratory/animal/field activities
    - documentation and evidence pertaining to (but not limited to)
        - institutional biosafety committee minutes
        - laboratory incident and accident reports
        - staff training and competency records
        - staff health records
        - risk assessments
        - infectious waste management records
        - primary and secondary biocontainment/ engineering maintenance records
    - biorepository information and accountability
- identification, regulation and education on matters of 'reverse genetics' and 'gain of function' of pathogens.

3.2 Understanding the origins of SARS-CoV-2

For the purpose of this report, the SAGO is offering preliminary recommendations to outline studies that are urgently needed to generate scientific evidence to better understand the origins of SARS-CoV-2. The SAGO reiterates that this is the first preliminary report to WHO and represents work that is ongoing and not yet complete. The work of the SAGO should be read as a work in progress. Further reports of the SAGO will be provided as discussions continue.

To this end, the SAGO, with the support of the WHO Secretariat, has been provided with the following information to inform technical discussions (a full list of presentations provided to members of the SAGO is provided in Annex 1):

- an overview of WHO's work on high-threat pathogens and other advisory groups and how their work relates to the SAGO
- an overview of the March 2021 WHO-convened global study of origins of SARS-CoV-2: China Part by a member of the international mission team
- the results of an ongoing systematic literature search conducted by WHO, and the organization of available published and pre-print research findings related to the origins of SARS-CoV-2

[1] Note: the Responsible Life Sciences Research for Global Health Security guidance document is currently under review for updating.

- summaries of findings, from ongoing reviews and technical consultations, in the form of presentations by the WHO Secretariat on the following topics:
    - overview of global surveillance and ongoing studies evaluating the potential presence of SARS-CoV-2 in biological samples in 2019, including follow-up studies and verification efforts by independent laboratories where potential SARS-CoV-2 was detected in biological materials
    - overview of SARS-CoV-2 and SARS-like virus circulation in animals globally
    - findings of research on SARS-CoV-2 susceptibility in animals
- presentations from invited Chinese scientists on research conducted since the publication in March 2021 of the WHO-convened global study of origins of SARS-CoV-2: China Part and the status of the implementation of the recommended studies from report, including topics of:
    - molecular epidemiology studies
    - serosurveys for SARS-CoV-2 among blood donors in Wuhan
    - animal and environmental studies
    - evidence for the cold chain in the introduction and transmission of SARS-CoV-2
- a presentation from a SAGO member from South Africa on the epidemiology and possible sources of emergence of the SARS-CoV-2 variant of concern Omicron.

Limitations

The SAGO was only able to assess information that has been made available to them through either published reports or presentations from invited scientists. When interpreting the available published studies that were conducted during the first phase of the outbreak, it is important to take into account temporal and contextual differences in case definitions of SARS-CoV-2 infection. There are also recognized challenges associated with data review and case re-interview such a long time after the initial outbreak. Not all of the studies presented by Chinese scientist are yet published and are therefore indicated as pre-prints or unpublished where a peer-reviewed report is not available. The SAGO has not evaluated any raw data. For all other technical areas in this report, the SAGO is focusing their work on peer reviewed published studies, while recognizing that there are numerous pre-print publications available. Although acknowledged, the SAGO has not included pre-prints in this report, with a few notable exceptions (these are clearly identified in this report). If pre-prints are later published in peer-reviewed journals, these findings will be taken into account in SAGO's future reports.

3.2.1 Summary background of the SAGO's understanding of available evidence on SARS-CoV-2 origins

The SAGO is in the process of evaluating findings of studies on the origins of SARS-CoV-2 using published literature. The work of the SAGO is not yet complete, and the SAGO is not able to identify any conclusive findings that lead to the origins of SARS-CoV-2. However, a brief summary on what is currently known about work related to the potential origin of the SARS-CoV-2 pandemic is provided below.

Early human studies

Many published studies, as well as findings presented in the WHO-convened global study of origins of SARS-CoV-2: China Part, have examined the initial reported cases of the SARS-CoV-2 pandemic that were identified in Wuhan. The case findings conducted in the early months of the pandemic (December 2019 - January 2020) identified COVID-19 cases with onset of symptoms starting from December 2019 (Huang et al., 2020). Some of these cases had exposure to the Huanan Seafood Market, some to other markets

in Wuhan and some had no history of exposure to any markets (Lu et al., 2020a)(Worobey et al., 2022)[2]. Most of the identified human cases at the beginning of the outbreak were those who presented with notable symptoms. There was, however, little information on, or detection of, those cases with mild disease or asymptomatic infection, due to the fact that surveillance systems were not designed to capture a substantial component of the spectrum of illness caused by SARS-CoV-2 infection, and early definitions may not have captured those mild cases/asymptomatic infections.

Early human samples showed that the SARS-CoV-2 virus strains from some of the cases linked to the Huanan market were identical or highly similar, suggesting the market may have been the source of an amplification event (Lu et al., 2020a). Analysis of the viral genome from early cases, however, also showed some degree of diversity, suggesting multiple introductions with several acquisitions from the source into the population and/or unrecognized circulation (Lu et al., 2020a). This finding does not imply that the market was the origin of SARS-CoV-2, however, it provides additional leads that need to be followed up on in order to identify the source of the early infections; including studies of the source of the environmental contamination, details of the specific animal species sold at the market that may have acted as intermediate hosts from where spill over may have occurred, the farms from where these animals originated, and studies (including serologic studies) of the vendors at the markets and workers at the farms. The SAGO acknowledges that several recent pre-print studies on this topic provide similar findings (Worobey et al., 2022) (Gao et al., 2022) (Pekar et al., 2022).

Animal studies

To date, neither the virus progenitors nor the natural/intermediate hosts have been identified. The current available data on the closest related SARS-like viruses and susceptibility of many animal species to SARS-CoV-2 suggest a zoonotic source. *Rhinolophus* bats, which carry betacoronaviruses with the largest known diversity, including viruses with proximity to SARS-CoV-2 strains detected in humans, are considered to be the most likely ancestral hosts (Table 1). However, the intermediate host(s), if any, and the characteristics of spillover events to humans is still unknown. For SARS-CoV, carnivores (civet cats, racoon dogs) were identified as intermediary hosts, setting an ecological precedent for the natural history of SARS-CoV-2 (Wang and Eaton, 2007).

Table 1 summarizes published findings of SARS-CoV-2-like viruses identified that are closely related to SARS-CoV-2. Notably, the most closely related genomic sequences have been found in bats, namely the Laos Banal-52 strain with 96.8% identity to the SARS-CoV-2 original Wuhan strains (Temmam et al., 2022), followed by RaTG13, with 96.1% identity, identified in China in 2013 (Zhou et al., 2020b). Laos Banal-52 is most closely related in its spike receptor binding domain (RBD). However, these viruses do not appear to be sufficiently closely related to SARS-CoV-2 to be identified as the immediate source of acquisition. There were also viruses isolated from pangolins in China in 2019 (showing a 92.4% or less identity) (Liu et al., 2019) making it unlikely that they are the intermediate host. More characterization of viral diversity, starting at the sources of these viruses, may provide further leads.

[2] Note: Worobey et al. has been made available as a pre-print and is not yet peer reviewed.

Table 1. SARS-CoV-2 related bat and pangolin coronaviruses

Animal Species	Virus strain	Genome Identity to SARS-CoV-2*	Originating region, country	Year identified	References
Bat (*Laotian R. malayanus*)	BANAL-52[2]	96.80%	Laos	2020	(Temmam et al., 2022)
Bat (*R. pusillus*)	BANAL-103	95.20%	Laos	2020	
Bat (*R. malayanus*)	BANAL-116	92.90%	Laos	2020	
Bat (*R. marshalli*)	BANAL-236	95.20%	Laos	2020	
Bat (*R. malayanus*)	BANAL-247	92.20%	Laos	2020	
Bat (*R. affinis*)	RaTG13	96.10%	Yunnan province, China	2013	(Zhou et al., 2020a)
Bat (*R. pusillus*)	RpYN06	94.48%	Yunnan province, China	2019	(Zhou et al., 2021)
Bat (*R. pusillus*)	RmYN02	93.30%	Yunnan province, China	2019	(Zhou et al., 2020a)
Bat (*R. shameli*)	RshSTT182	92.90%	Cambodia	2010	(Delaune et al., 2021)
Bat (R. shameli)	RshSTT200	92.90%	Cambodia	2010	
Malayan pangolin (*Manis javanica*)	PCoV-GDC	92.40%	Unknown (seized during anti-smuggling operation in China)	2019	(Xiao et al., 2020) (Liu et al., 2020) (Zhou et al., 2020a)
Bat (*R.acuminatus*)	RacCS203	91.15%	Thailand	2020	(Wacharapluesadee et al., 2021)
Bat (*R. pusillus*)	PrC31	90.70%	Yunnan province, China	2018	(Li et al., 2021)
Malayan pangolin (*Manis javanica*)	PCoV-2020	90.32%	Unknown (seized during anti-smuggling operation in China)	2019	(Liu et al., 2020)
Malayan pangolin (*Manis javanica*)	MP789	90.20%	Unknown (seized during anti-smuggling operation in China)	2019	(Liu et al., 2019)

*N.B. The table includes studies with genome identity above 90%

According to a published survey of animals sold at the Huanan Market between 2017 and 2019, several species known to be susceptible to SARS-CoV-2 (such as raccoon dogs (*Nyctereutes procyonoide*), red foxes (*Vulpes vulpes*) and others) were present in the Huanan market (Xiao et al., 2021). However, it is noted by the SAGO that those animals were not sampled in the studies presented to the SAGO by invited Chinese scientists. The findings in Xiao et al. also correlate with a recent pre-print publication including information about animals identified at the Huanan market (Worobey et al., 2022). Further information about studies into the testing of these animals, the tracing back of these animals to source farms and serologic investigations into people who farmed and sold/traded these animals have been requested to China. Any additional findings related to these studies will be further discussed in future SAGO meetings.

According to the presentations offered by the invited Chinese scientists to the SAGO, the following studies have been performed since the WHO-convened global study of origins of SARS-CoV-2: China Part (noting that much of this material is unpublished). Included in the data presented to the SAGO by

scientists from the Chinese Academy of Medical Sciences, Chinese Academy of Sciences and the National Institute for Viral Disease Control and Prevention, China CDC on 14 January 2022, was:

- A survey of bat coronaviruses identifying 146 new bat sarbecoviruses in China and no SARS-CoV-2-related virus (Wu et al., 2021)[3].
- SARS-CoV-2-related virus strains identified in Laos, Thailand and Cambodia, the closest being BANAL-52 (Temmam et al., 2022), suggesting that further studies in the Indochina Peninsula of South-East Asia and in the southwest border area of China, where RaTG13 was identified, are needed (Zhou et al., 2021).
- A survey of pangolin coronaviruses conducted on 163 pangolins seized during anti-smuggling operations in China identified SARS-CoV-2-related viruses with 86.3% similarity. Samples from 2019, which were seized by Guangdong customs, showed 90% similarity with the human SARS-CoV-2 strains from 2020, while others seized by Guang Xi customs from 2017 had 85% similarity but showed the highest homology with the SARS-CoV-2 S protein among the current cultivable viruses. (Liu et al., 2020)
- A survey of known SARS-CoV-2 susceptible animals finding that Canine coronavirus in raccoon dogs in Changli and Leting in Hebei Province had a 94% identity (compared to the index virus) however, there were no positive SARS-CoV-2 samples captured (unpublished data presented to the SAGO).
- Initial animal testing of 32 479 animal samples (species and numbers of species were not specified) from 18 provinces in China, did not find any nucleic acid-positive tests for SARS-CoV-2.
  - Serologic results from 1211 serum samples from livestock and poultry and 2837 serum samples from dogs, cats, mink, foxes and racoons were presented suggesting no positive results for SARS-CoV-2 antibodies (unpublished data presented to the SAGO).
  - Results from an initial sampling study carried out in 31 provinces in China of over 80 000 animal samples (species and numbers of species were not specified) suggesting no positive results for SARS-CoV-2 infection were found (unpublished data presented to the SAGO).[4]
  - Results from an environmental sampling conducted in the Huanan market produced 73 positive samples for SARS-CoV-2 samples of the 923 environmental samples tested, but no SARS-CoV-2 samples were detected among 18 species of animals from the market. As recommended in the 2021 WHO-China Joint Report, the animal barcode (potential host RNA abundance) in the positive environmental samples were further analyzed; and a link was found between the positive environmental samples and human RNA (Gao et al., 2022) [3].
  - Results from a meta transcriptomic analysis conducted on 1941 game animals from artificial breeding sites that supply animal markets and zoos across China. Results presented to the SAGO suggested that no SARS-CoV-2 or SARS-CoV-related sequences were identified (He et al., 2022).

Animals susceptible to SARS-CoV-2

Throughout 2020 and 2021, a number of studies evaluated SARS-CoV-2 susceptibility in animals. The results of these are summarized in Tables 2.A and 2.B. Table 2.A shows susceptible animals identified through experimental means. Table 2.B shows a list of additional hosts which have been identified through reverse zoonotic infections and have expanded our knowledge of susceptible animals that should be investigated as possible intermediate hosts.

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[3] Studies are still in pre-print format and have not yet been peer-reviewed. The SAGO awaits peer-reviewed published studies to be made available to provide a proper assessment.

[4] WHO-convened global study of origins of SARS-CoV-2: China Part

Table 2. A. Susceptible animals to SARS-CoV-2 identified through experimental means*

Animal Species	Susceptibility (a)	Intra-species transmission**	Reference
African green monkeys (*Chlorocebus aethiops*)	Yes	Not specified	(Blair et al., 2021)
Baboons (*Papio hamadryas*)	Yes	Not specified	(Singh et al., 2021)
Bank voles (*Myodes glareolus*)	Yes	No	(Ulrich et al., 2021)
Bushy-tailed woodrats (*Neotoma cinerea*)	Yes	Not specified	(Bosco-Lauth et al., 2021a)
Campbell's dwarf hamster (*Phodopus campbelli*)	Yes	Not specified	(Trimpert et al., 2020)
Cat (*Felis silvestris catus*)	Yes	Yes	(Rudd et al., 2021; Shi et al., 2020; Porter et al., 2022)
Cattle (*Bos taurus*)	Yes (Low susceptibility)	No	(Ulrich et al., 2020; Bosco-Lauth et al., 2021b)
Chinese hamster (*Cricetulus griseus*)	Yes	Not specified	(Bertzbach et al., 2021)
Common marmosets (*Callithrix jacchus*)	Yes	Not specified	(Lu et al., 2020b)
Cynomolgus macaques (*Macaca fascicularis*)	Yes	Not specified	(Salguero et al., 2021; Lu et al., 2020b)
Deer mice (*Peromyscus maniculatus*)	Yes	Yes	(Bosco-Lauth et al., 2021a; Fagre et al., 2020)
Dog (*Canis lupus familiaris*)	Yes (Low susceptibility)	No	(Shi et al., 2020; Bosco-Lauth et al., 2020;Sit et al., 2020)
Egyptian fruit bat (*Rousettus aegyptiacus*)	Yes	Yes	(Schlottau et al., 2020)
Ferret (*Mustela furo*)	Yes	Yes	
Goat (*Capra hircus*)	Yes (Low susceptibility)	Not specified	(Bosco-Lauth et al., 2021a)
Mice - BALB/c and C57BL/6 *	Yes	Yes (mouse adapted)	(Shuai et al., 2021; Montagutelli et al., 2021)
Mice - Transgenic hACE2*	Yes	Not specified	
Mink (*Neovison vison*)	Yes	Yes	(Shuai et al., 2020)
Pig (*Sus scrofa domesticus*)	Yes (Low susceptibility)	No	(Pickering et al., 2020; Vergara-Alert et al., 2021))
Rabbit (*Oryctolagus cuniculus*)	Yes	Not specified	(Mykytyn et al., 2021)
Raccoon dogs (*Nyctereutes procyonoide*)	Yes	Yes	(Freuling et al., 2020)
Rat - Sprague Dawley*	Yes	Not specified	(Shuai et al., 2021)
Red Fox (*Vulpes vulpes*)	Yes	Not specified	(Porter et al., 2022)
Rhesus macaques (*Macaca mulatta*)	Yes	Not specified	(Salguero et al., 2021; Munster et al., 2020)
Roborovski hamster (*Phodopus roborovskii)*	Yes	Not specified	(Trimpert et al., 2020)
Sheep (*Ovis aries*)	Yes (Low susceptibility)	No	(Gaudreault et al., 2021)
Striped skunks (*Mephitis mephitis*)	Yes	Not specified	(Bosco-Lauth et al., 2021a)
Syrian hamster (*Mesocricetus auratus)*	Yes	yes	(Sia et al., 2020; Imai et al., 2020)
Crab-eating macaque (*Macaca fascicularis*)	Yes	Not specified	(Böszörményi et al., 2021)
Tree shrews (*Tupaia belangeri chinensis*)	Yes	Not specified	(Xu et al., 2020; Zhao et al., 2020)
White-tailed deer (*Odocoileus virginianus*)	Yes	Yes	(Palmer et al., 2021)
Winter white dwarf hamster (*Phodopus sungorus*)	Yes	Not specified	(Trimpert et al., 2020)
Zebra fish (*Danio rerio*)	Yes	Not specified	(Laghi et al., 2021)
Zebra mussel (*Dreissena polymorpha*)	Yes	Not specified	(Le Guernic et al., 2021)

Animal Species	Susceptibility (a)	Intra-species transmission**	Reference
Animals tested and found to not be susceptible to SARS-CoV-2			
Alpaca (*Lama pacos*)	No	-	(Bosco-Lauth et al., 2021b)
Black-tailed prairie dogs *(C. ludovicianus)*	No	-	(Bosco-Lauth et al., 2021a)
Chicken – Duck – Geese – Turkey (*Gallus gallus domesticus, Anas platyrhinchos domesticus, Anser cygnoides, Meleagris gallopavo)*	No	-	(Schlottau et al., 2020) (Suarez et al., 2020)
Coyotes (*Canis latrans*)	No	-	(Porter et al., 2022)
Fox squirrels (*Sciurus niger*)	No	-	(Bosco-Lauth et al., 2021a)
Horse (*Equus ferus caballus*)	No	-	(Bosco-Lauth et al., 2021b)
House mouse (*Mus musculus)*	No	-	(Bosco-Lauth et al., 2021a)
Midge (*Culicoides sonorensis*)	No	-	(Balaraman et al., 2020)
Mosquitoes (*Aedes aegypti, Aedes albopictus, Culex quinquefasciatus*)	No	-	
Quail (*Coturnix japonica*)	No		(Suarez et al., 2020)
Racoons (*Procyon lotor*)	No	-	(Bosco-Lauth et al., 2021a)
Wyoming ground squirrels (*Urocitellus elegans*)	No	-	

* Laboratory bred strains for experiments
(a*) Proof of infection; (b) Main symptoms*
References for this table are adapted from OIE WAHIS reporting system.
**Not specified means not having proof of transmission.

Table 2. B. Susceptible animals to SARS-CoV-2 identified through natural infections*

Animal (species)	Susceptibility	Intra-species transmission	Country (ies) of detection	Location of transmission
Asian small-clawed otters (*Aonyx cinereus*)	Yes	Not specified	United States of America	Aquarium Zoo
Binturong (Arctictis *binturong)*	Yes	Not specified	United States of America	Zoo
Canada Lynx *(Lynx canadensis)*	Yes	Not specified	United States of America	Zoo
Coatimundi (*Nasua nasua*)	Yes	Not specified	United States of America	Zoo
Domestic American Mink *(Neovison vison)*	Yes	Yes (Lu et al., 2021) (Munnink et al., 2021)	Canada, Denmark, France, Greece, Italy, Latvia, Lithuania Netherlands, Poland, Spain, Sweden	Farm
Domestic cat *(Felis catus)*	Yes	Not specified	United States of America, Argentina, Belgium, Brazil, Canada, Croatia, Chile, Estonia, France, Finland, Germany, Greece, Hong Kong SAR, Italy, Japan, Russia, Spain, Switzerland, the United Kingdom, Uruguay, Iran	Household

Animal (species)	**Susceptibility**	**Intra-species transmission**	**Country (ies) of detection**	**Location of transmission**
Domestic Dogs *(Canis lupus familiaris)*	Yes	Not specified	United States of America, Argentina, Bosnia and Herzegovina, Brazil, Canada, Croatia, Denmark, France, Hong Kong SAR, Japan, Mexico, Myanmar, Switzerland, Uruguay, Finland	Household
Domestic Ferret *(Mustela furo)*	Yes	Not specified	United States of America, Slovenia	Household
Fishing cat (*Prionailurus . viverrinus)*	Yes	Not specified	United States of America	Zoo
Hamster (unspecified)	Yes	Yes (Yen et al., 2022)	Hong Kong SAR	Pet shop Warehouse of pets
Lion *(Panthera leo)*	Yes	Not specified	United States of America, Croatia, Colombia, Estonia, Singapore, South Africa, Spain, Sweden	Zoo
Puma *(Puma concolor)*	Yes	Not specified	United States of America, Argentina, South Africa	Wild animal exhibitor facility Rescue centre; Zoo
Snow Leopard (*Panthera uncia)*	Yes	Not specified	United States of America	Zoo
Spotted hyenas *(Crocuta crocuta)*	Yes	Not specified	United States of America	Zoo
Tiger *(Panthera tigris)*	Yes	Not specified	United States of America, Denmark, Indonesia, Sweden, United Kingdom	Animal sanctuary Zoo Wild animal exhibitor facility
Western lowland Gorilla *(Gorilla gorilla)*	Yes	Yes (Kalema-Zikusoka et al., 2021)	United States of America	Zoo
White-tailed deer (*Odocoileus virginianus*)	Yes	Yes (Chandler et al., 2021) (Martins et al., 2021)	United States of America, Canada	Natural Park Wild habitat
Wild American Mink *(Neovison vison)*	Yes	Not specified	United States of America, Spain	Free range
Wild Leopard (*Panthera pardus fusca)*	Yes	Not specified	India	Free range

*References for this table are adapted from OIE WAHIS reporting system, and FAO report.
(OIE, 2022) (FAO, 2022)

Retrospective studies

The SAGO has begun to evaluate studies that have published results indicating SARS-CoV-2 positive samples collected prior to December 2019. Table 3 lists studies that have suggested the possible detection of SARS-CoV-2 in stored samples prior to the start of the outbreak in those countries. The SAGO notes that the methods of each study with results indicating positive samples in 2019 requires further validation and verification and thus the significance of these findings remains unclear. The SAGO is currently reviewing these studies and the methods used to identify the positive samples and will provide further information in forthcoming reports to WHO.

Table 3. Studies* that tested pre-pandemic samples for SARS-CoV-2 early occurrence

*This list should be considered preliminary and may not be a complete record of studies available. At the present time, only peer reviewed published papers were included in this report. The SAGO notes several studies available as pre-prints that have not yet undergone peer-review and/or verification.

Pre-pandemic samples tested (published studies)							
Country	**Study period of the samples**	**Sample type**	**Results for samples**	**Number of positive samples (date of earliest detection)**	**Number of samples tested**	**Technology used to analyse samples**	**Reference**
Italy	December 2019	Sewage	Positive	15 (2 earliest date to December 2019)	NA	nested RT-PCR and RT-PCR	(La Rosa et al., 2021)
	September 2019 - March 2020	Blood	Positive for SARS-COV-2 antibodies	111 of 959 showed SARS-COV-2 antibodies (September 2019). 6 of 111 positive through microneutralization test (October 2019)	959 111	RBD-ELISA/microneutralization assay	(Apolone et al., 2021)*
	November 2019	Skin biopsy	Positive	1 (November 2019)	1	RT-PCR (negative); RNA fluo-rescence *in situ* hybridization (positive)	Research letter (Gianotti et al., 2021)
	November 2019 - March 2020	Plasma	Positive	11 (November 2019)	290 (234 liver diseases, 56 blood donors)	Antibody RDT + CLIA No neutraliza-tion assay	(Gragnani et al., 2021)

Pre-pandemic samples tested (published studies)							
Country	**Study period of the samples**	**Sample type**	**Results for samples**	**Number of positive samples (date of earliest detection)**	**Number of samples tested**	**Technology used to analyse samples**	**Reference**
	September 2019– February 2020	Throat swab	Positive	1 (December 2019)	39	RT-PCR	(Amendola et al., 2021)
France	November 2019 -March 2020	Serum samples	Positive	13 (November – December 2019)	9,144	ELISA + Neutraliza-tion assay	(Carrat et al., 2021)
	December 2019 – January 2020	Respiratory samples	Positive	1 (December 2019)	14	RT-PCR	(Deslandes et al., 2020)
USA	Oct 2019 - March 2020	Nasopharyn geal swabs	Positive	7 (mid-January 2020)	2,321	RT-PCR	(Hilt et al., 2022)
	January 2020 -March 2020	Blood	Positive	9 (January 2020)	24,079	ELISA	(Althoff et al., 2021)
	December 2019 - January 2020	Blood	Positive	106 (reactive) of 7389 samples (mid December 2019). 84 of 90 had neutralizing activity (mid-December 2019).	7,389 total blood donation collected 90 further tested (ELISA/m icroneutr alisation	ELISA/ microneu-tralization assay	(Basavaraju et al., 2021)
	2011-2020	Serum samples from wild deer	Positive	3 – (2020 samples) 1 – (2019 sample - at limit of detection, not confirmed by another virus neutralisation test) 0 (from 2011 – 2018)	239	Surrogate virus neutralizatio n assay	(Chandler et al., 2021)

Pre-pandemic samples tested (published studies)							
Country	**Study period of the samples**	**Sample type**	**Results for samples**	**Number of positive samples (date of earliest detection)**	**Number of samples tested**	**Technology used to analyse samples**	**Reference**
Norway	December 2019 - December 2020	Serum samples from pregnant women	Positive	36 (1 from December 2019)	6,520	eCLIA + CLIA No Neutraliza-tion assay	(Eskild et al., 2022)
Pre-pandemic samples tested but found to be negative for SARS-CoV-2							
Country	**Study period**	**Sample type**	**Results for samples**	**Number of positive samples**	**Number of samples tested**	**Technology used to analyse samples**	**Reference**
Canada	January-February 2020	Respiratory specimens, patients with ILI	Negative	NA	1,440	RT-PCR	(Xiong et al., 2020)
	August 2019	Wastewater	Negative	NA	NA	RT-PCR	(D'aoust et al., 2021)
Germany	December 2019 – April 2020	Respiratory specimens	Negative	NA	195	RT-PCR	(Panning et al., 2020)
	December 2019 – January 2020	Respiratory specimens, patients with ILI	Negative	NA	260	RT-PCR	(Eberle et al., 2021)
Italy	November 2019 – March 2020	Respiratory specimens	Negative	NA	166	RT-PCR	(Capalbo et al., 2020)
	December 2019 – March 2020	Respiratory specimens	Negative	NA	906	RT-PCR	(Calderaro et al., 2021)
	November 2019 – March 2020	Respiratory specimens, pediatric patients ILI	Negative	NA	293	RT-PCR	(Rizzo et al., 2021)
	October 2019-February 2020	Respiratory specimens, patients with ILI	Negative	NA	1,224 (601 in 2019)	RT-PCR	(Giardina et al., 2021)
Japan	Influenza season 2019/2020	Respiratory specimens, patients with ILI	Negative	NA	182	RT-PCR	(Kaku et al., 2021)

Pre-pandemic samples tested (published studies)							
Country	**Study period of the samples**	**Sample type**	**Results for samples**	**Number of positive samples (date of earliest detection)**	**Number of samples tested**	**Technology used to analyse samples**	**Reference**
Scotland	December 2019 – February 2020	Respiratory specimens, ICU patients	Negative	NA	148	RT-PCR	(Tomb et al., 2020)
United Kingdom	January-March 2020	Respiratory specimens, patients with ILI	Negative before February 2020	NA	1,378	RT-PCR	(Chappell et al., 2021)
United States	January – April 2020	Wastewater	Negative before 21 January 2020	NA	NA	RT-PCR	(Sherchan et al., 2020)
Spain	November-mid March	Combined nasopharyngeal and oropharyngeal swabs	Negative	NA	1,823	RT-PCR	(Mira-Iglesias et al., 2022)
Italy	Mid November 2019-April 2020	Nasopharyngeal swabs	Negative	NA	631	RT-PCR	(Galli et al., 2021)
Italy	1st November 2019 and 29th February 2020	Oropharyngeal swabs	Negative	NA	1,683	RT-PCR	(Panatto et al., 2021)

*The WHO Secretariat has been in discussions to initiate technical collaborations with the researchers responsible for this work and a separate laboratory for verification and validation of the results included in the publication referenced. This work is ongoing.

**The SAGO acknowledges that there are additional studies that are not yet published. The SAGO will wait for peer-reviewed publications of those articles and will work to further review those and other additional studies.

As previously reported in the in the WHO-convened global study of origins of SARS-CoV-2: China Part report, an initial high level review was presented to the mission team including over 76 000 patients presenting to 233 health institutions in Wuhan in the months before the recognized outbreak in December 2019. The results presented to the WHO mission team visiting China in January - February 2021 suggest that none of the 76 000 patients were compatible with COVID-19. As was suggested in the Joint Report, the SAGO recommends more work needs to be done to evaluate the criteria used to disregard these 76 000 as SARS-CoV-2 cases. For example, as the SARS-CoV-2 case definition was initially very stringent during this first review, this likely resulted in many asymptomatic, mild to moderate COVID-19 cases being missed. In 2021, the joint WHO-China team recommended that a further review be made of the methods used to identify and characterize the initial patients in the retrospective clinical

search for patients presenting with relevant conditions to the 233 Wuhan medical institutions, in order to search for features (such as clustering) that could be suggestive of occurrence of previously unrecognized cases of SARS-CoV-2 infection. They recommended a new undertaking of this review and agreed on a new, broader case definition. It is possible that the application of stringent clinical criteria, resulting in the identification of only 92 clinically compatible cases, may have decreased the possibility of identifying a group or groups of cases with milder illness. Furthermore, the possibility that earlier transmission of SARS-CoV-2 infection was occurring in this community cannot be excluded on the basis of this evidence or lack thereof. The SAGO renews this recommendation and suggests a further review is required to study these 76 000 patients and their potential link to the early days of the COVID-19 pandemic.

Based on data presented by invited Chinese scientists to the SAGO; a descriptive review of surveillance data for ILI, pharmacy purchases and analyses of mortality data did not provide clear evidence of widespread circulation of SARS-CoV-2 before the recognized start in December 2019. The SAGO is awaiting further details on the unexplained increase in ILI in adults from Wuhan the 46th week of 2019, preceding increases seen in ILI in Wuhan in the 51st and 52nd weeks of 2019. Additional analytical approaches may be able to identify differences from expected normal patterns, including comparisons of data from different provinces in China and to previous years.

The SAGO was also presented with new unpublished serologic results by Chinese scientists of more than 40 000 stored samples from blood donors in Wuhan who provided blood between September and December 2019 (Chang et al., 2022). These samples were reported to have been tested for antibodies to SARS-CoV-2. More than 200 samples proved positive (by ELISA), however, none were positive upon using a confirmative assay (by serum neutralization assays). Other samples collected in Wuhan prior to December 2019 were reported to be negative on retrospective serological testing. The SAGO has requested further information on these data and the methods used to analyze these samples.

In addition, the SAGO has reviewed publications with findings of SARS-CoV-2 detection in biological and environmental samples in 2019 from different parts of the world (Table 3). In some cases, such as in Italy, France and the United States, verification and/or validation has been initiated by WHO through the help of external laboratories. This work is currently ongoing (Montomoli et al., 2021). The SAGO supports further investigations in any part of the world where there is firm evidence of SARS-CoV-2 virus activity before the recognized outbreak in Wuhan in December 2019. This should also be considered in other areas where there has been evidence of early SARS-CoV-2 activity (see some examples of studies in Table 3).

Possibility of introduction of SARS-CoV-2 to the human population through a laboratory incident

The SAGO recognizes the work of the joint WHO-China team and the findings presented in their report. During the discussions of the SAGO, the SAGO has agreed, apart from three objections (see footnote)[5], that it remains important to consider all reasonable scientific data that is available either through

[5] It is noted that three members of SAGO (Dr Vladimir Dedkov, Dr Carlos Morel, Professor Yungui Yang) do not agree with the inclusion of further studies evaluating the possibility of introduction of SARS-CoV-2 to the human population through a laboratory incident in this preliminary report due to the fact that from their viewpoint, there is no new scientific evidence to question the conclusion of the WHO-convened global study of origins of SARS-CoV-2: China Part mission report published in March 2021.

published or other official sources to evaluate the possibility of the introduction of SARS-CoV-2 into the human population through a laboratory incident.

To support biosafety and biosecurity investigations into the introduction of SARS-CoV-2 into the human population through a laboratory incident; the SAGO notes that there would need to be access to and review of the evidence of all laboratory activities (both *in vitro* and *in vivo* studies) with coronaviruses including SARS-CoV-2-related viruses or close ancestors and the laboratory's approach to implementation and improvement of laboratory biosafety and biosecurity. As it is not common practice to publish the institutional implementation of biosafety and biosecurity practices of individual laboratories in peer-reviewed scientific journals, additional information will need to be obtained and reviewed to make conclusive recommendations.

3.2.2 Preliminary recommendations on further investigations of COVID-19 origins

Based on discussions to date, the SAGO offers the following preliminary recommendations organized by elements that are included in the global framework (described above):

- early investigation studies
- genomic and molecular epidemiological investigations
- assessing the possibility of the introduction of SARS-CoV-2 to the human population through an animal or environmental spillover event
- assessing the possibility of the introduction of SARS-CoV-2 to the human population through a breach in biosafety and biosecurity measures through a laboratory incident.

The SAGO's recommended studies to WHO should be used as guidance for further investigation of the origins of SARS-CoV-2 as One Health collaborations between human, animal and environmental scientist as stated in the SAGO framework.

Early investigation studies

The initial recommended studies addressing the early investigations of the pandemic are as follows (but are not limited to):

- Additional studies of potential cases in 2019 in Wuhan are needed from China and should include a further review, including analyses of clinical and demographic characteristics and risk factors among the initial 174 human cases identified in China.
- Further review should be conducted by Chinese scientists and collaborators of the methods used to identify and characterize the cases in the retrospective clinical search for patients presenting with relevant conditions to the 233 Wuhan medical institutions to search for features (such as clustering) that could be suggestive of occurrence of previously unrecognized cases of SARS-CoV-2 infection.
- Explore the availability of human samples collected in the months running up to the emergence of SARS-COV-2 for other health programmes (e.g. polio and measles surveillance) in China as well as public health entities in other parts of the world and test them for SARS-CoV-2 presence through PCR or serological testing.[6]
- Conduct a time-series analyses on the weekly influenza-like illness (ILI) data from 2019 in Wuhan, China, in comparison to earlier years. ILI data should also be examined from additional Chinese

provinces and National Influenza Centers or other surveillance programs in other parts of the world where there may have been evidence of early SARS-CoV-2 activity.[7]

- A review should be conducted of pharmacy purchases, and other similar metrics, during the September to December 2019 period compared to the same periods in 2016, 2017 and 2018 to look for any signals of increased purchases in China and other parts of the world. Any signals identified should be followed by analyses for spatial-temporal clusters. This investigation should include examination of surveillance data in the period prior to December 2019 looking for signs of compatible clinical activity and combined where appropriate with a search for relevant stored clinical samples and testing using harmonized/validated methods.[8]

Genomic and molecular epidemiological investigations

The initial recommended genomics and molecular epidemiology studies needed are as follows (but are not limited to):

- Combine molecular and global distribution data and other metadata of potentially relevant animal hosts. This will be important because many coronaviruses that are phylogenetically related to SARS-CoV-2 have been discovered from *Rhinolophus* species (horseshoe bats) around the world, particularly in Asia, including South-East Asia, where retrospective tests of samples collected from *Rhinolophus* bats should be conducted.
- Continue analyses of the global SARS-CoV-2 genome and raw sequences with epidemiological and clinical data and link the analysis results. Genomics research should integrate raw sequencing reads, genome sequences and metadata (including onset and sampling date and sampling location) of early cases. Bioinformatics analyses should be performed, including sequence variant identification, haplotype network construction, phylogenetic analysis and time to the most recent common ancestor (tMRCA) analysis.
- Monitor the GISAID and GenBank comprehensive information databases and combine molecular data, global distribution data and other metadata of potential animal hosts. To date, GISAID collects the largest number of SARS-CoV-2 genomes and supports many databases and computational tools and has become an import hub in genomic surveillance. Thanks to the massive sequences collected in GISAID, GenBank and databases, the introduction and transmission of SARS-CoV-2 has been successfully revealed in many countries. Moreover, new variants of concern were discovered through analyses of GISAID and GenBank data.
- Investigate the data on the sequences of receptor binding site (ACE-2 receptor) and other elements (furin cleavage sites) and potential recombination with different variants or other coronaviruses to determine origins and potential roles in enhancing transmission to humans. SARS-CoV-2 presents a mosaic genome contributed to by different progenitors. The origin of several fragments of SARS-CoV-2 genomes could be assigned to several donor strains from bats rather than a unique donor sequence.
- With WHO coordination, a comprehensive verification exercise of any detection of SARS-CoV-2 from biological samples from 2019 should be continued worldwide.

Assessing the possibility of the introduction of SARS-CoV-2 to the human population through an animal or environmental spill over event

The initial recommended animal and environmental studies are as follows (but are not limited to):

[6,7,8] WHO-convened global study of origins of SARS-CoV-2: China Part

- Studying the chain of interspecies transmission may or may not involve one or more domestic animal species or farmed wild species. There is a need to study the path taken by the virus from its ancestral host to humans, accounting for the viral genomic evolution occurring through each step. Studies must include direct and indirect interface with wild animals, direct interface with domestic animals infected with pathogens from wild or domestic animals and chains of transmission between ancestral hosts and intermediate species. Increase surveillance in wildlife is needed globally where SARS-like viruses were detected in bats as well as susceptible species detected through reverse zoonoses to detect potential current and future animal reservoirs.
- SAGO acknowledges the effort already invested in the screening of animal species with a potential to act as intermediary hosts for the virus. Even if large numbers of animals were tested in some geographical areas, the investigations in China should be better focused to include relevant mammalian target species, considering prior knowledge on disease ecology, particularly for SARS-CoV-2/SARS-CoV-like viruses. More focus is needed on studies involving carnivores in China, particularly those kept or bred in larger numbers for human exploitation, such as for food or fur production (racoon dogs, civet cats, mink) in different countries and regions.
- It is essential to determine husbandry sites that are sources of supply for the Huanan Seafood Market and other wet markets in Wuhan. Studies should include validation of laboratory methods, sampling method (including number of samples), positive controls such as by detection of other viruses in sample collections and sharing of voucher samples and sub-samples of tested specimens with international laboratories. Investigations and audits should be carried out to determine the places and sizes of such breeding sites.
- There should be particular attention to culling activities before or after the first detection of SARS-CoV-2 in humans. Animal products, either preserved (dry, smoked, fermented, sausages, etc.) or potentially stored from culling activities or animal products from the period before the outbreak should be identified and tested. Humans employed in breeding facilities or in the downstream exploitation chain should be identified and serologically tested. Sera from such persons should be shared with international laboratories for external verification.

The initial recommended studies to carry out are as follows (but are not limited to):

- Conduct retrospective surveys including testing for SARS-CoV-2 from animals and animal products supplied to Wuhan markets in 2019, if such samples are still available.
- In testing of potential animal reservoir hosts, including intermediate hosts, it is advisable to specifically investigate sequences of the receptor binding site (ACE-2 receptor), the polybasic furin recognition motif at the S1/S2 domain border and other elements typical for SARS-CoV-2 that could have contributed to the formation of the latter by processes of recombination or sequential mutation.
- Investigate the possible role of the cold-chain process in the introduction of the virus to the market and/or human population, to identify whether the products entered the cold-chain contaminated or whether an ineffective cold-chain allowed them to become contaminated along the way to the market. In particular, sampling of animals from the source farms from where the products originated needs to be conducted to determine whether the animals themselves were positive for SARS-CoV-2 or the virus was introduced at a later stage. Studies should also follow the route of transmission within the market to better assess whether the introduction of the virus came about by an infected human or contaminated product.

- Analyse virus persistence and viability of SARS-CoV-2 at different temperatures to simulate the freeze-thaw cycle that would happen naturally as products are shipped from one port to another, then through the supply chain.
- Analyse the persistence and survival of SARS-CoV-2 in environmental farming samples (e.g. wastewater, mink farm waste and the surrounding environment).
- Conduct traceability research on the suspected origin of SARS-CoV-2. For example, conduct traceability research on countries and regions with reported positive results in sewage, serum, human or animal tissues/swabs and other SARS-CoV-2 tests by the end of 2019.
- To obtain a better overview of potential target regions for studies inside and outside southern China, it is advisable to combine molecular and global distribution data and other metadata of potentially relevant animal hosts.
- Coronaviruses phylogenetically related to SARS-CoV-2 have been discovered in *Rhinolophus* species (horseshoe bats) around the world, particularly in South-East Asia. Retrospective tests of samples collected from *Rhinolophus* bats should be carried out globally and in particular in Asia and South-East Asia.
- Conduct a behavioral risk study on the human-animal-environment interface of the Huanan market workers, vendors and Hunan community, including infected and noninfected groups, from September to December 2019.

Possibility of Introduction of SARS-CoV-2 to the human population through a laboratory incident

Initial recommendations for assessing the possibility of the introduction of SARS-CoV-2 to the human population through a breach in biosafety and biosecurity measures through a laboratory incident are as follows (but are not limited to):

- Additional investigations should be carried out with the staff in the laboratories tasked with managing and implementing biosafety and biosecurity at laboratories: (1) those in the proximity of the original COVID-19 outbreak working with SARS-like viruses in Wuhan, China and potentially with (2) those located worldwide where early COVID-19 cases have been retrospectively detected before 2020. The rationale is as follows:
    - This would provide an opportunity for more specific questions to be asked related to biosafety and biosecurity management of SARS-like virus studies at the individual laboratories.
    - This would provide an opportunity for staff and scientists to give their perspective on the possibility of a laboratory incident and whether any occupational illnesses occurred before the recognized start of the pandemic.

- The scope of the discussions and investigations should include the following recommendations where the first cases were reported in China:
    - Examine regulatory biosafety or biocontainment standards and biocontainment levels and risk-mitigation strategies for SARS-like CoV-associated studies. These considerations should include discussions with those responsible for administering biosafety and biosecurity.
    - Determine the occupational hazards intrinsic to laboratories working with SARS-like CoV and the nature of the studies performed before the first reported COVID-19 cases in Wuhan and whether they involved reverse engineering or gain-of-function, genetic manipulation or animal studies with strains of SARS-like CoV.

- Determine the risks associated with field-related activities, such as the collection of specimens from bats or other wildlife sources and the potential for SARS-like CoV infection of staff.
- Evaluate potential scenarios where a breakdown in biosafety or biosecurity procedures led to a possible laboratory-acquired infection with the studied pathogen.
- Determine if there were any reported biocontainment breaches or laboratory incidents or accidents with SARS-like coronaviruses in biosafety level (BSL2/3/4) laboratories that may have resulted in escape and/or infection of staff members prior to December 2019 where early cases were detected in China.

3.3. Studies on the emergence of new variants of SARS-CoV-2

The SAGO also considered expanding discussions surrounding the global framework to the emergence of other high threat pathogens and in particular, SARS-CoV-2 variants of concern, which are outlined on the WHO webpage for tracking SARS-CoV-2 variants.

Since SARS-CoV-2 was first identified, several variants of concern have been identified. New variants will continue to emerge, but several epidemiological factors determine whether they become variants of concern and flourish in a vulnerable population. This may include viral factors that increase transmissibility or pathogenicity, overcome population immunity (whether derived from vaccination and/or infection) through positive selection and genetic drift, the lack of other competing variants at the end of epidemic waves and the country's capacity to detect such variants through genomic surveillance capacity. The SAGO notes that is important that countries not be discouraged from reporting new variants and to keep in mind that the detection of new variants does not necessarily equate with the emergence of a variant from their region. In the current context, the SAGO discussed applying the framework to the most recent SARS-CoV-2 variant of concern, Omicron. The group reviewed the available evidence and identified three hypotheses that could explain the development of Omicron, all of which should be investigated.

One possibility is emergence of the variant in under-studied populations living in countries where testing and genomic surveillance are low. Second, given the high number of mutations identified in Omicron, it may have evolved in immune-suppressed hosts, such as people living with HIV who have high viral loads or cancer patients. The third hypothesis is evolution in animals following reverse zoonosis. SARS-CoV-2 has been shown to infect many species of wild and domestic animals (reported in above sections of this report). Although none of the strains identified in animals to date are similar to those in humans, genomes from animals are significantly underrepresented on GISAID, with ~2000 sequences from animals of the >11 million genomes submitted.

Initial recommended studies are as follows (but are not limited to):

- Enhance genomic surveillance by sequencing cases worldwide to identify the earliest detected cases to determine where and when the variant first emerged and enhance genomic surveillance in under-represented areas. This necessitates funding support for genomic surveillance in under-resourced areas.
- Increase investigation and surveillance worldwide in immune-supressed individuals, including people living with HIV and people who have cancer or who are otherwise immune suppressed;

and ensure sustained antiretroviral treatment for people living with HIV, while being mindful of further stigmatizing these high-risk populations.
- Enhance animal surveillance for reverse zoonoses, including in mammalian wildlife and species with frequent human contact, such as rodents and domestic species; and increase One Health investigations.
- Perform routine surveillance of sewage and wastewater for early prediction of the emergence of variants.
- Collate data on population immunity in the period that immediately preceded the emergence of new variants in the areas where they first emerge.

4. Next steps

The SAGO is committed to the work outlined in the terms of reference and will continue to further develop and outline elements of the global framework and provide specific and detailed recommendations to inform future investigations into the origins of emerging and re-emerging pathogens. The SAGO will also identify and evaluate available tools and make recommendations for new tools needed to support specific recommended studies, investigations and evaluations.

Regarding SARS-CoV-2 origins, the SAGO will continue to review all available findings from current and new studies. It will further outline what is currently known and identify gaps where specific studies are urgently needed to provide evidence to better understand the origins of this pathogen.

As a next step, the SAGO will have their first in person meeting on 1-2 June 2022 at the WHO headquarters in Geneva. This meeting will provide an opportunity to meet face to face for the first time. The specific objectives for the meeting are still being developed (at the time of writing) but will focus on discussions and development of a work plan for the next year of work according to the SAGO TOR.

In addition, the SAGO will continue to meet virtually to advance their work. Future meetings of the SAGO will address advancing the preliminary recommendations in this report through gathering of further scientific evidence as it becomes available and engaging with relevant experts globally to help facilitate further investigations that will inform recommendations to WHO.

Proposed topics for future meetings include:

- Further analysis of findings from studies pertaining to the Huanan market in Wuhan China and follow up on any identified leads.
- Global engagement with scientists working on SARS-like viruses in bats to seek input on the molecular biology and evolution of these viruses and to identify potential biosafety issues.
- In-depth investigation of animals susceptible to SARS-CoV-2, surveillance and retrospective testing of samples to identify the possible intermediate hosts and potential new animal reservoirs.
- Review of available literature (both published and unpublished studies) on early cases and surveillance samples that tested positive for COVID-19 before December 2019
- Outline studies on the origins of new variants for testing of the major hypotheses. This will include collaborations with other experts working on genomic surveillance, wastewater surveillance, and surveillance in immunosuppressed patients and potential animal reservoirs.

- Discussions about the studies needed to study the re-emergence of other high threat pathogens, e.g., monkeypox virus, MERS-CoV, arboviruses, Ebola virus.

Future reports from the SAGO will include a summary of what is currently known and not known about the origins of SARS-CoV-2 and what the scientific community can do to address these gaps.

Per the terms of reference of the SAGO, this scientific advisory group will continue to be a resource that WHO calls upon every time there is a need to evaluate an emerging or re-emerging pathogen in the world. This group, which brings together individuals with widely diverse specialties and a vast amount of experience in emerging infectious diseases and pandemic preparedness, plans to serve WHO in its advisory role for years to come.

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Annexes

Annex 1. SAGO Members

This full list of SAGO members can be found online on the SAGO webpage.

1. **Chair: Marietjie Venter** is a professor in medical virology at the University of Pretoria, South Africa. She leads the zoonotic Arbovirus and Respiratory Virus Research Programme Centre for Viral Zoonoses, at the Department of Medical Virology at the University of Pretoria.
2. **Vice-chair: Dr Jean-Claude Manuguerra** is the research director at the Environment and Infectious Risks Unit which also covers a laboratory for biological threats, as well as the national reference centre for hantaviruses at the Institut Pasteur, France.
3. **Mr Phillip Alviola** is an Associate Professor in the Animal Biology Division at the Institute of Biological Sciences, University of Philippines. Has experience working in bat ecology, surveillance and virology for over 20 years. Focuses on coronaviruses and hantaviruses.
4. **Dr Abdullah Assiri** is the Assistant Deputy Minister for Preventative Health at the Ministry of Health in Saudi Arabia. His past experience is also with the Saudi Arabia Ministry of Health mainly in Infection Prevention and Control. He is part of the IHR Emergency Committee on MERS-CoV and was heavily involved in the initial descriptions of MERS-CoV in Saudi Arabia.
5. **Dr Stuart Blacksell** is a Professor of Tropical Microbiology at the Nuffield Department of Medicine, University of Oxford. He is a Biosafety expert who works in Thailand. Expertise in biosafety across a broad network and working in high containment settings. He is also a member of the WHO biosafety advisory group member of the editorial committee of the WHO authority biosafety manual fourth edition. As well as a member of the WHO COVID-19 IHR Emergency Committee.
6. **Dr Inger Damon** is a Director of the Division of High Consequence Pathogens and Pathology at the United States Centers for Disease Control and Prevention in the USA. Works on a broad and diverse array of pathogens from filoviruses to the viral hemorrhagic viruses. She has extensive experience in ebola, marburg, rabies, meliodosis, anthrax, and poxviruses. Interested in understanding the origins of introductions of these diseases and how sequencing can support our understanding through a one health approach of how pathogens move from reservoirs to intermediate hosts and ultimately to humans.
7. **Dr Vladimir Dedkov** is the Deputy Director for Research at the Pasteur Institute in Russia. His main interests are in molecular epidemiology. He was one of the original mission team members of the WHO team that went to Wuhan to investigate SARS-CoV-2.
8. **Dr Christian Drosten** is a professor and head of the Institute of Virology at Charité in Germany. He is originally from Germany.
9. **Dr Elmoubasher Farag** is a Senior Infectious Diseases Epidemiologist and the Head of Communicable Diseases Control Programs at the Ministry of Public Health in Qatar. He has experience in the investigations into the initial cases of MERS-CoV, as well as SARS-CoV-2. He is most Interested in understanding how to utilize a one-health approach to outbreak response. He was one of the original mission team members of the WHO team that went to Wuhan to investigate SARS-CoV-2.
10. **Dr Thea K Fischer** is a professor of virology at the University of Copenhagen, and the head of clinical research, at the Nordsjaellands Hospital. Her main research interests are in in prevention and control of common viruses and preparedness and response to epidemics/pandemics. She was one of the original mission team members of the WHO team that went to Wuhan to investigate SARS-CoV-2.

11. **Dr Raman Gangakhedkar** is the Dr C.G. Pandit National Chair of the Indian Council of Medical Research. He has previously worked as a clinician and epidemiologist in HIV. He was involved in 2018 Nipah outbreak in Kerala, India. As well as the Zika outbreak and COVID-19 outbreak in India.
12. **Dr Nada Ghosn** is the Head of the Epidemiology Surveillance Program at the Ministry of Health in Lebanon. She works on COVID-19 surveillance, polio, influenza, and ebola.
13. **Dr Maria Guzman** is the Head of the Center for Research, Diagnostic and Reference at the Institute of Tropical Medicine Pedro Kouri in Cuba. She has experience working on dengue, zika, chikungunya, influenza, and COVID-19. Interested in the pathogenesis and epidemiology of diseases. Member of the Arbovirus Technical Advisory Group (TAG).
14. **Dr Christian Happi** is Professor and director at the African Center of Excellence for Genomics of Infectious Disease (ACEGID), Redeemer's University, Ede, Nigeria. He is originally from Cameroon.
15. **Dr Gladys Kalema-Zikusoka** is Founder and Chief Executive Officer of an NGO -Conservation Through Public Health, which investigates diseases between endangered gorillas and people and other diseases at the human/wildlife/livestock interface. She works closely with the Uganda Ministry of Health and sits on the task force for marburg, ebola, anthrax, and COVID-19. Also works on behaviour change communication with communities in wildlife rich habitats.
16. **Dr Normand Labbé** is currently a Biosafety Inspector at the Public Health Agency of Canada. He is interested in understanding how to do research safely.
17. **Dr Sowath Ly** is the Deputy Health of Epidemiology and Public Health Unit at the Instiut Pasteur du Cambodge. He has a background in medical epidemiology. He is involved in research and studies on infectious diseases such as dengue, chikungunya, and rabies.
18. **Dr Khin Myint** is a Senior Researcher in the Emerging Virus Research Unit at the Eijkman Institute for Molecular Biology in Jakarta, Indonesia. She has spent over 30 years working on arboviruses and respiratory viral pathogens. She is most interested in understanding spillover events that lead to emerging viruses .
19. **Dr Carlos Morel** is the Director for the Center for Technological Development in Health at the Oswaldo Crus Foundation (Fiocruz) and Ministry of Health in Brazil. He has a background in molecular parasitology. Since his work on Zika in 2014, he has become interested in emerging infectious diseases and in particular COVID-19, chikungunya, and biosafety. Interested in the need for expanding appropriate biosafety laboratory capacity, surveillance and disease X.
20. **Dr Hung Nguyen–Viet** is the co-program leader of the Animal and Human Health Program at the International Livestock Research Institute, Kenya. He is a microbiologist working on the intersection of animal and human health. Interested in zoonotic diseases and food safety such as food markets in resource limited countries. He was one of the original mission team members of the WHO team that went to Wuhan to investigate SARS-CoV-2.
21. **Dr Chinwe Ochu** is the Director of the Prevention Programmes and Knowledge Management at the Nigeria Centre for Disease Control. She is a public health specialist who supervises infection prevention and control and antimicrobial programme, as well as the COVID-19. Is also the technical lead for national emerging Viral Hemorrhagic Disease group.
22. **Dr Masayuki Saijo** is the Director of the Medical affairs as part of the Sapporo City Health and Welfare Bureau. He is the chief officer for the Welfare Bureau for the COVID-19 response. He has experience in emerging virus infections and re-emerging infections including viral hemorrhagic fevers.

23. **Dr Rosemary Sang** is the Advisor and Chief Research Officer at the Centre for Virus Research at the Kenya Medical Research Institute (KEMRI). She has a background in entomology and medical biology and understanding of arbovirus transmission.
24. **Dr Katharina Sumermatter** is the Head of the Biosafety Center at the Institute for Infectious Diseases, University of Bern. Background in biosafety and biosecurity. Has been involved in the national reference center for highly contagious animal diseases and emerging zoonotic diseases. Has been involved in the WHO biosafety lab biosafety manual for WHO.
25. **Dr Supaporn** Wacharapluesadee is an emerging infectious diseases Researcher at the Thai Red Cross Emerging Infectious Diseases Clinical Center, King Chulalongkorn Memorial Hospital and Thai Red Cross Society Committee member of Chula School of Global Health, Faculty of Medicine at the Chulalongkorn University in Thailand. She has experience in leading the team that directed first MERS-CoV and COVID-19 in Thailand.
26. **Dr John Watson** is a former clinician and public health specialist, and now an Honorary Professor at the Faculty of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine. He is also a visiting Professor, Research Department of Infection and Population Health, at University College London. He has worked in infectious disease epidemiology and outbreak response. He has been a member of the WHO advisory group for pandemic influenza. He was one of the original mission team members of the WHO team that went to Wuhan to investigate SARS-CoV-2.
27. **Dr Yungui Yang** is the Deputy Director of the Beijing Institute of Genomics at the Chinese Academy of Sciences. His expertise is in research Bioinformatics, genomics and biology. Studies the lifecycle of coronaviruses such as SARS-CoV-2. Also participated in the WHO joint mission to China, on the China part.

Annex 2. Plenary meetings of the SAGO 2021-2022

	SAGO Meeting Dates	Presentations the SAGO received
1	**23 November 2021 (first meeting)**	• WHO's processes of setting up an advisory group and the way they are expected to function from legal, ethical and communications viewpoints • An overview of WHO's work in high threat pathogens, including SARS, MERS, VHF, Arboviruses, COVID-19, • An overview of WHO's work in biosafety and biosecurity and its potential collaboration with the TAG-Biosafety.
2	**9 December 2021**	• A review of the findings and recommendations from the March 2021 Joint WHO-China mission report by one of the mission members (a SAGO member) • Status of implementation and findings of the recommended studies outlined in the March 2021 Joint China-WHO March mission report from Chinese Scientists.
3	**15 December 2021**	• Overview of pre-pandemic 2019 studies currently available in published evidence and WHO's role on validation and follow up • Overview of SARS-CoV-2 and SARS-CoV-like virus circulation in animals by a member of the WHO Secretariat • Overview of Omicron emergence by a SAGO Member.
4	**14 January 2022**	• Presentation by Chinese Scientists on an update on the implementation of studies recommended in the 2021 WHO-China Joint report.
5	**19 January 2022**	• Secretariat presented on the ongoing literature review looking at the published literature on the origins of SARS-CoV-2 • Secretariat presented on the animal susceptibility studies currently published or underway.
6	**31 January 2022**	• Members discussed their input into the first preliminary SAGO report.
7	**14 February 2022**	• Members reviewed the first preliminary SAGO report and discussed input.
8	**10 March 2022**	• Members reviewed the first preliminary SAGO report and discussed input.
9	**8 April 2022**	• Members reviewed the first preliminary SAGO report and finalized input into the report.

Annex 3. Letters of request from the SAGO/WHO to China for information on the studies of SARS-CoV-2 origins conducted in China

Letter 1. SAGO request to China, 30 November 2021.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences
Department of Medical Virology

Pretoria
South Africa
30 November 2021

WHO SAGO secretariat

Dear Dr Van Kerkhove and SAGO Secretariat,

In my capacity as chair of the SAGO, I would like to bring to your attention the discussions held during the first meeting on the 23 November 2021 with regards to objective 4 in the terms of reference pertaining to SAGO's role in advising WHO in the context of SARS-CoV-2 origins.

In order to move ahead with this objective, the group identified the need for an update on the phase two studies identified in the Joint Report on the WHO-convened Global Study of Origins of SARS-CoV-2. This will enable the group to better inform WHO on the next series of studies needed to explore the origins of SARS-CoV-2.

On behalf of the SAGO, we would hereby like to request WHO to ask China to provide WHO and the SAGO with an update on the implementation of the phase two studies into the origins of the SARS-CoV-2 virus as outlined in the Joint Report at the next SAGO meeting, which is planned for December 9th 12:00-14:00CET.

Best wishes

Yours sincerely,

Professor Marietjie Venter
Chair of the Scientific Advisory Group on the Origins of Novel Pathogens, WHO
Head of the Zoonotic Arbo- and Respiratory virus Research programme
Centre for Viral Zoonosis
Department Medical Virology
University of Pretoria,
South Africa

Room 2.68, Centre for Viral Zoonoses, Department Medical Virology, Faculty of Health
University of Pretoria, PO BOX2034
Arcadia, Pretoria, 0001, South Africa
Tel +27 (0)12 319 2636
Email marietjie.venter@up.ac.za
www.up.ac.za

Fakulteit Gesondheidswetenskappe
Departement Mediese Virologie
Lefapha la Disaense tša Maphelo
Kgoro ya Virolotši ya Kalafo

Letter 2. SAGO request to China, 9 December 2021.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences
Department of Medical Virology

Pretoria
South Africa
9 December 2021

Dear Dr Maria Van Kerkhove and WHO SAGO Secretariat,

In my capacity as chair of the SAGO, I would like to pass along our thanks to Professor Yigang Tong for the presentation at the SAGO meeting on 9 December 2021.

With regards to the SAGO TOR's Objective 4, in order for the SAGO to be able to advise the WHO on the prioritization of future studies to investigate the SARS-CoV-2 origins it first needs to understand the current state of studies being conducted in pursuit of the origins of SARS-CoV-2, and in particular the status of the studies that were recommended by the joint WHO-China Mission team in March 2021.

The SAGO would therefore like to make a follow-up request to the one made to you via letter on 30 November 2021, to ask China to provide **a short report in writing** that provides WHO and the SAGO specifically with an update on the status and implementation of the studies that were recommended in the *WHO Concerned Global Study Joint Report* (p 53, 87, and 109).

This includes an update, specifically on which studies have been undertaken, the timing of when they will be finished, and any findings on human and molecular epidemiology studies, as well as animal, food and environmental studies. We are looking for a written update of the recommended studies summarised in slides 21- 25 in the attached presentation from the 2nd SAGO meeting on 9 December 2021, where these recommended studies were mentioned.

The next SAGO meeting, is planned for 15 December 12:00-14:00CET, we will appreciate if this report can reach us by this date. We request that this written response be provided in English if possible, for SAGO members to review by the next meeting on 15 December 2021, and that our Chinese colleagues would be available for any questions at the next meeting in January 2022.

We thank the Chinese colleagues once again for their presentation today and further collaborations.

Best wishes,

Professor Marietjie Venter
Chair of the Scientific Advisory Group on the Origins of Novel Pathogens, WHO
Head of the Zoonotic Arbo- and Respiratory virus Research programme
Centre for Viral Zoonosis
Department Medical Virology
University of Pretoria,
South Africa

Room 2.68, Centre for Viral Zoonoses, Department Medical Virology, Faculty of Health
University of Pretoria, PO BOX2034
Arcadia, Pretoria, 0001, South Africa
Tel +27 (0)12 319 2636
Email marietjie.venter@up.ac.za
www.up.ac.za

Fakulteit Gesondheidswetenskappe
Departement Mediese Virologie
Lefapha la Disaense tša Maphelo
Kgoro ya Virolotši ya Kalafo